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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,760	11/19/2001	Shohei Koide	176/60901 (6-11402-968)	2042

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Michael L. Goldman
NIXON PEABODY LLP
Clinton Square
P.O. Box 31051
Rochester, NY 14603

EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,760	KOIDE, SHOHEI	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 109-184* is/are pending in the application.

4a) Of the above claim(s) *109-184* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

The Art Unit and Examiner prosecuting this application have been changed. Any inquiries relating to the examination of the application should be directed to Shulamith H. Shafer, Art Unit 1647.

Applicants amendments and remarks of 4 April 2006, in response to the 31 October 2005 Office Action, are acknowledged and have been entered. The declaration of Shohei Koide (under 37 CFR § 1.132) has been entered.

Claims 1-16 and 180-184 are pending in the instant application. Claims 1, 9, 12 and 115 have been amended and amendments have been entered. New claims 180-184 have been added and entered.

Claims 109-179 were withdrawn in the previous office action of 31 October 2005 as being directed to an invention that is independent or distinct from the invention originally claimed. Applicants traverse this withdrawal (Remarks of 4 April 2006, page 16, 3rd paragraph) as applied to claims 109-121 and 138-144, drawn to compositions and kits respectively. The reasons for traversal are that Claims 109-121 and 138-144 are related to Claim 16 as combination-subcombination, and therefore restriction is not proper between these claims. Applicant's arguments have been fully considered but are not found to be persuasive for reasons of record and those presented below. Claims 1-16 are directed to a single polypeptide either a fibronectin type III polypeptide monobody (Claim 1) or a fusion protein comprising a polypeptide monobody of Claim 1 (Claim 16). Claims 109-121 recite an *in vivo* composition comprising the fusion polypeptide of claim 16 and a second fusion polypeptide; Claims 138-144 are drawn to a kit comprising a culture system containing at least one transformed host cell comprising a reporter gene, a fusion polypeptide according to claim 16, and a fusion protein comprising a nuclear receptor or fragment thereof. Each of these inventions is distinct from the invention as originally claimed since they recite at least one additional protein. This additional polypeptide comprises a target protein, wherein said target

protein comprises a nuclear receptor including ligand-binding domain. The presence of an additional polypeptide in the composition or kit would necessitate an additional search of relevant literature in many different areas of subject matter, as these claims also require certain functional activities. Furthermore, Claim 109 recites an *in vivo* composition; the term *in vivo* could reasonably be interpreted as a composition for administration to an organism for therapeutic or diagnostic purposes. This would thus entail a search for an appropriate subject population. The searches for these inventions would not be co-extensive with the search of the originally claimed invention (Claims 1-16) and would present a serious burden on the Office.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 122-179 remain withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Newly presented claims 180-184 recite a myriad of amino sequences not previously presented. The request is not timely and searching for these newly presented sequences, each representing a polypeptide of a unique structure and function, at this stage of prosecution would present a serious burden to the Office. Therefore, claims 180-184 are withdrawn from consideration.

Claims 1-16 are under consideration. Claims 17-108 are cancelled. Claims 109-184 are withdrawn from consideration.

The pertinent remarks/arguments filed with the amendment received 4 April 2006 will be responded to herein. The text of those sections of Title 35 U.S. Code not included in this action can be found in the prior Office action.

Reinstated and/or Maintained Rejections

Double Patenting

Upon further consideration, the rejection of Claims 1-16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 or U.S. Patent No. 6,673,901 is reinstated. This rejection was originally made in the Office Action of 19 April 2005 and withdrawn in the Office Action of 31 October 2005.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of the '901 patent for reasons of record, stated in the Office Action of 19 April 2005. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over,

the reference claim(s). See, for example, *In re Berg*, 140 F.3d 1428 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claim 1 of the '901 patent is drawn to a fibronectin type III (Fn3) polypeptide monobody comprising at least two Fn3 β-strand domain sequences with a loop region region which varies as compared to the wild type (SEQ ID NO:110) loop region sequence by deletion, insertion or replacement of at least two amino acids in the loop region sequence. Claim 1 of the instant invention recites a fibronectin type III (Fn3) polypeptide monobody comprising at least two Fn3 β-strand domain sequences with a loop region sequence that varies by deletion, insertion or replacement of at least two amino acids from a corresponding loop region, N-terminal tail or C-terminal tail in a tenth Fn3 domain of fibronectin. The specification discloses that one preferred wild-type Fn3 scaffold is the tenth Fn3 domain of human fibronectin (FNfn10) which has an amino acid sequence according to SEQ ID NO:2. The monobody of claim 1 of the '901 patent differs from the monobody claim of the instant invention in that the instant claims do not recite that the wild-sequence is SEQ ID NO:110. Claim 1 of the '901 patent does not recite a monobody that exhibits nuclear receptor binding, nor does it recite a fusion protein comprising a polypeptide monobody. The instant claimed monobody is an obvious variation of the claim as set forth in the '901 patent for the following reasons. The specification of the '901 teaches a synthetic gene for tenth Fn3 of human fibronection was designed (column 11, lines 46-47). This synthetic gene is identified as encoding an amino acid sequence of SEQ ID NO:110 (column 7, line 41). The '901 patent further discloses fusion proteins comprising monobodies and his tags (column 13, line 40-43). Applicant is reminded that those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent (In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970), MPEP 804).

Applicants traverse this rejection in Remarks of 15 August 2005 (page 15, 3rd-6th paragraph bridging page 16, 1st paragraph). The traversal is on the grounds that the

'901 patent fails to teach or suggest all the claim limitations of the instant invention. Applicants assert that Claim 1 of the '901 patent fails to explicitly claim monobodies that exhibit nuclear receptor binding affinity. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. Claim 1 of the '901 patent recites a fibronectin type III (Fn3) polypeptide monobody that binds to a specific binding partner (SBP) to form a polypeptide:SBP complex. Claim 1 and the specification of the '901 patent fail to further define, or identify examples of "specific binding partner". A specific binding partner would inherently encompass a myriad of binding partners including a "nuclear receptor". Thus, "nuclear receptor" is a subset of the larger set of "specific binding partner. The rejection is reinstated.

35 U.S.C. § 112, First Paragraph

The rejection of Claims 1-16 under 35 U.S.C. 112, first paragraph for not being enabled for the full scope of the claims is maintained for reasons of record (Office Action of 31 October 2005) and those detailed below.

The specification, while being enabling for a fibronectin type III (Fn3) polypeptide monobody comprising:

at least two Fn3 β-strand domain sequences with a loop region sequence linked between adjacent β-strand domain sequences; and

optionally, an N-terminal tail of at least about 2 amino acids, a C-terminal tail of at least about 2 amino acids, or both;

wherein at least one loop region sequence, the N-terminal tail, or the C-terminal tail comprises an amino acid sequence which varies by deletion, insertion or replacement of at least two amino acids from a corresponding loop region, N-terminal tail, or C-terminal tail in a tenth Fn3 domain of fibronectin of **SEQ ID NO:2** or the mutant Fn 3 scaffold of the tenth Fn3 domain of fibronectin which has a modified Asp7

(which is replaced by a non-negatively charged amino acid residue) of **SEQ ID NO:3**, and

wherein the polypeptide monobody exhibits nuclear receptor binding activity

does not reasonably provide enablement for a fibronectin type III (Fn3) polypeptide monobody comprising:

at least two Fn3 β-strand domain sequences with a loop region sequence linked between adjacent β-strand domain sequences; and

optionally, an N-terminal tail of at least about 2 amino acids, a C-terminal tail of at least about 2 amino acids, or both;

wherein at least one loop region sequence, the N-terminal tail, or the C-terminal tail comprises an amino acid sequence which varies by deletion, insertion or replacement of at least two amino acids from a corresponding loop region, N-terminal tail, or C-terminal tail in **any** tenth Fn3 domain of fibronectin and

wherein the polypeptide monobody exhibits nuclear receptor binding activity

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants traverse this rejection (page 17, 3rd paragraph of Remarks of 4 April 2006). Applicants have submitted Declaration of Shohei Koide as evidence in support of this traversal. The remarks of 4 April 2006 are basically identical to those submitted in the declaration and thus, the two will be addressed together.

Applicants traverse the rejection on the basis that:

1. The tenth Fn3 domain amino acid sequences exhibit a high degree of identity and conservation and therefore a person of skill in the art would fully expect mammalian tenth Fn3 domains that are highly similar to the human Fn3 domain to be useful as a starting scaffold for preparing functional polypeptide monobodies that bind to a nuclear receptor of interest.

2. The PTO has cited the teachings Garcia-Pardo et al. (1985, J Biol Chem 260:10320-10325) that applicants assert are irrelevant to the claimed invention because the region of fibronectin that was analyzed by Garcia-Pardo is distinct of the tenth Fn3 domain that is used as a starting scaffold for preparing the claimed monobodies.

3. The PTO has cited evidence of mutational instability of proteins other than the tenth Fn3 domain of fibronectin.

4. The application teaches how to perform a library selection to obtain only monobodies that exhibit nuclear receptor binding affinity.

Applicant's arguments have been fully considered and have been found to be persuasive, in part, for the following reasons.

The Office finds the argument that the teachings of Garcia-Pardo et al. are irrelevant to the claimed invention persuasive in that the 31-kDa fragment taught by Garcia-Pardo et al. is not an Fn3 domain and contains disulfide bonds, not contained in the Fn3 domain of the monobody of the instant invention. However, the scope of enablement rejection is still maintained.

While it is true that the mammalian tenth Fn3 domain is 86-100% conserved relative to the human Fn3 sequence of SEQ ID NO:2 (Declaration of Shohei Koide, 5th paragraph, and Remarks of 4 April 2006, page 17, 2nd paragraph), the most highly conserved regions are the β-strand sequences. The specification teaches that it is the loop region sequences that are rendered capable of binding to a nuclear receptor by deletion, insertion, or replacement of at least two regions from a corresponding loop region. The loop regions have a higher degree of variability than do the β-strand sequences (Declaration of Shohei Koide, 5th paragraph, and Remarks of 4 April 2006, page 17, 2nd paragraph). Applicants have not disclosed which portions of a given loop sequence, ie which amino acid positions, must be maintained, and which may be changed to render the monobody capable of binding nuclear receptors. While the starting scaffold may be disclosed, insufficient guidance is presented in the specification as to the changes which may or may not be made in the loop sequences that would result in a monobody capable of binding a nuclear receptor, or a nuclear receptor that

has bound a particular agonist or class of agonists, or a nuclear receptor which has been bound by a particular antagonist or class of antagonists. The monobodies of the instant invention could potentially bind proteins other that the nuclear receptor. Karastan et al. (2004, Chemistry and Biology 11:835-844) teach a monobody based on human tenth FN3 domain gene (page 641, column 2, 2nd paragraph). These monobodies bound to the SH3 domain of the human oncogenic protein, c-Src. Thus, these monobodies may bind any number of proteins of widely diverse biological activity. Absent sufficient guidance as to which amino acids in which of the loops of the monobody could be altered, undue experimentation would be required to make the monobodies that specifically bind nuclear hormones.

Applicants traverse the citation of evidence of mutational instability of proteins cited in Mickle et al (2000, Med. Clin. North Am. 84:597-607), Voet et al (1990, Biochemistry pp 126-128, 230) and Yan et al. (2000, Science 290:523-527) on the basis that these references are not relevant to the protein scaffold of the instant invention, based on the tenth Fn3 domain of fibronectin (Declaration of Shohei Koide, 9th paragraph, and Remarks of 4 April 2006, page 18, 1st paragraph). Applicants cite Voet et al (2004, Biochemistry, page 186) to assert that mutational changes may not cause significant physiological changes in the function of the protein. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. The exemplary protein cited by Voet et al. (2004) is cytochrome c. Applicants have not provided evidence that this protein is any more relevant to the tenth Fn3 domain of fibronectin than the proteins described by Mickle et al., Voet et al (1990) and Yan et al.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of

binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, Merz et al., eds, Birkhauser, Boston, pp. 491-495). Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Applicants assert that in the context of the present invention, mutational effects are not unpredictable since the present application teaches how to perform a library selection to obtain only monobodies that would exhibit nuclear receptor binding affinity (Declaration of Shohei Koide, 10th paragraph, and Remarks of 4 April 2006, page 18, 2nd paragraph). Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. Absent evidence to the contrary, one would not be able to predict which mutational effects would result in proteins that retain the activity of binding nuclear receptors. As noted above, the specification only teaches how to screen for claimed monobodies and test for functional variants.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives based on variants of any tenth Fn3 domain and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to provide activity, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The rejection of Claims 1-16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record (Office Action of 31 October 2005) and those stated below. Applicants traverse this rejection (Remarks of 4 April 2006, page 19, 1st-4th paragraph) on the grounds that applicant has identified a wild type (SEQ ID NO:2) sequence and over 50 mutant sequences derived therefrom and has asserted that the mammalian tenth Fn3 domain are not highly variant. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. As discussed above, the most highly conserved regions of the mammalian tenth Fn3 domain are the β-strand sequences. However, the specification teaches that it is the loop region sequences that are rendered capable of binding to a nuclear receptor by deletion, insertion, or replacement of at least two regions from a corresponding loop region. The loop regions have a higher degree of variability than do the β-strand sequences. The tenth Fn3 domain can vary based not only on allelic variations, but also according to species and allelic variants within the other species. The specification and claims do not indicate what distinguishing attributes must be shared by the members of the genus. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. There is no description of the conserved loops which are critical to the structure and function of the genus claimed. There is no description of which amino acid sites must be preserved in order to identify the monobodies encompassed by the claimed invention, monobodies which exhibit nuclear receptor binding activity.

Therefore, only monobodies constructed based on sequences of SEQ ID NOs 2 or 3, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Conclusions:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS

Brenda Brumback
BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600